NOVEL METHODS FOR THE PREPARATION
## OF TAXANES USING OXAZOLIDINE INTERMEDIATES

5   This is a division of 09/315,712, May 20, 1999,
allowed, which is a continuation of 08/845,299, April 25,
1997, abandoned which is a continuation of 08/408,676, March
22, 1995, abandoned.


Field of the Invention

10   The present invention relates to novel oxazolidines
which find utility as intermediates in the preparation of C-
13 acyloxy sidechain-bearing taxanes such as paclitaxel and
analogs thereof. The present invention also relates to
novel methods of preparing the oxazolidines, as well as to
15 novel methods of coupling the oxazolidines to form the
aforementioned sidechain-bearing taxanes.

Background of the Invention

        Taxanes are diterpene compounds finding utility in
20 the pharmaceutical field. For example, paclitaxel (Taxol®),
a taxane having the structure:
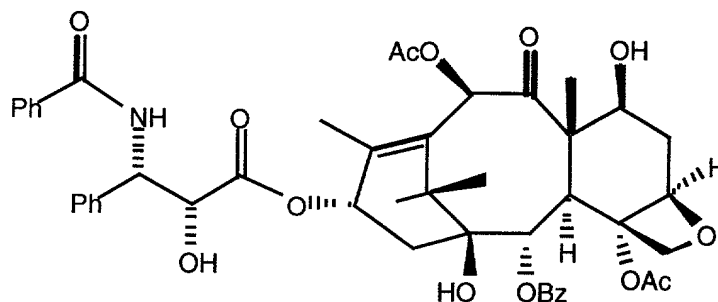
25 where Ph is phenyl, Ac is acetyl and Bz is benzoyl, has been
found to be an effective anticancer agent. The compound
taxotere, having the following structure, has also been
reported for anticancer use:

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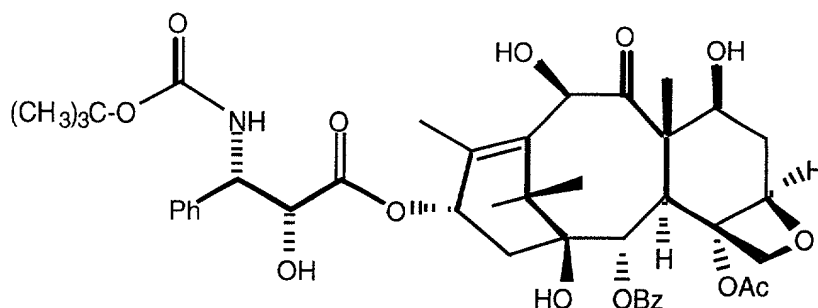
Naturally occurring taxanes such as paclitaxel may be found in plant materials, and have been isolated therefrom. Such taxanes may, however, be present in plant materials in

5   relatively small amounts so that, in the case of paclitaxel, for example, large numbers of the slow-growing yew trees forming a source for the compound may be required. The art has thus continued to search for synthetic, including semi-synthetic routes for the preparation of naturally occurring

10   taxanes such as paclitaxel, as well as routes for the preparation of pharmaceutically useful analogs thereof. In particular, efficient methods for the addition of a C-13 acyloxy sidechain to a taxane core are sought as the presence of the C-13 acyloxy sidechain imparts

15   pharmacological activity or provides a taxane more readily converted to one having such pharmacological activity.

Summary of the Invention

The present invention provides novel oxazolidine

20   compounds useful as intermediates for the preparation of C-13 acyloxy sidechain-bearing taxanes. Novel methods for coupling the oxazolidine intermediates of the invention with taxanes containing a hydroxyl group directly bonded at C-13 to provide the aforementioned C-13 acyloxy sidechain-bearing

25   taxanes are also provided, as are methods of preparing the novel oxazolidines of the present invention.

In particular, novel oxazolidines of the formulae I and II are provided:

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$$\text{(I)}$$

$$\text{(II)}$$
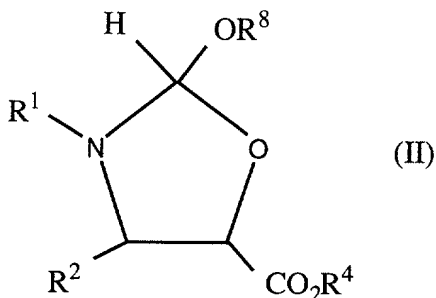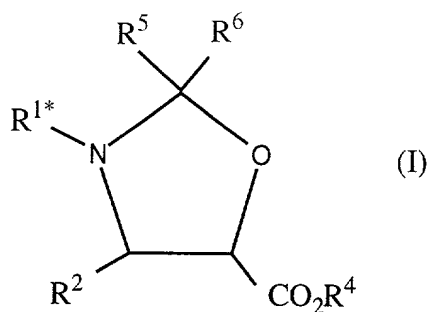
5 where

R^1 is hydrogen, arylcarbonyl, alkoxycarbonyl or
     alkylcarbonyl;

R^{1*} is hydrogen, arylcarbonyl, alkoxycarbonyl or
     alkylcarbonyl, with the proviso that R^{1*} is not

10   tert-butoxycarbonyl when R^2 is aryl;

R^2 is aryl, heterocyclo or alkyl;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, aryl,
   cycloalkyl, cycloalkenyl, or heterocyclo;

R^5 and R^6 are (a) each independently alkyl; or (b) together

15   with the carbon atom to which they are bonded, form a
     cycloalkyl, cycloalkenyl or heterocyclo group; and

R^8 is alkyl or aryl;
          and salts thereof.

          The novel oxazolidines of the present invention are

20 useful as intermediates in the preparation of C-13 acyloxy
sidechain-bearing taxanes such as paclitaxel and analogs
thereof. Thus, the present invention further provides novel

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methods for coupling the intermediates of the formulae I and
II with a taxane containing a hydroxyl group directly bonded
at C-13 to provide C-13 acyloxy sidechain-bearing taxanes of
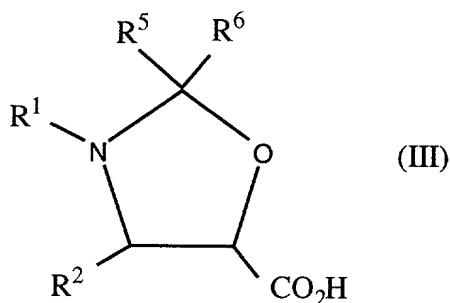the following formula VI:

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(VI)
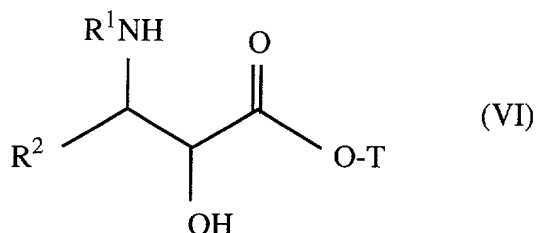
where R^1 is hydrogen, arylcarbonyl, alkoxycarbonyl or

alkylcarbonyl; R^2 is aryl, heterocyclo or alkyl; and T is a

10   taxane moiety directly bonded at C-13 of said moiety.
Coupling may be achieved by the methods described following.
      In one embodiment of the invention, a compound of the
formula VI or salt thereof may be prepared by a method
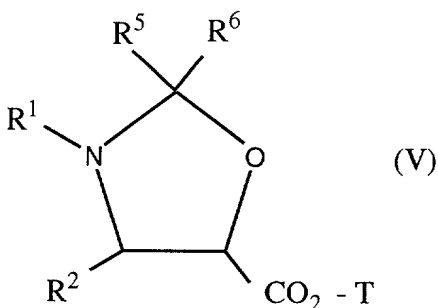comprising the steps of:

15   (a)   contacting a compound of the following
formula III or salt thereof:

(III)

,

20   with a compound of the following formula IV:

HO – T   (IV),

4

in the presence of a coupling agent, to form a compound of the following formula V or salt thereof:

$$\underset{R^2}{\overset{R^5 \quad R^6}{\underset{N}{\overset{R^1}{\diagdown}}}} \quad CO_2\text{-}T$$

(V)

5

where R^1, R^2, R^5, R^6 and T are as defined above; and

(b)   contacting said compound of the formula V or salt thereof with a ring-opening agent to form said compound of the formula VI or salt thereof. Each of the steps (a)

10 (when R^1 is R^{1*}) and (b) of this method are themselves novel methods. Additionally, the compounds of the formulae III and V and salts thereof are novel when R^1 is R^{1*}.
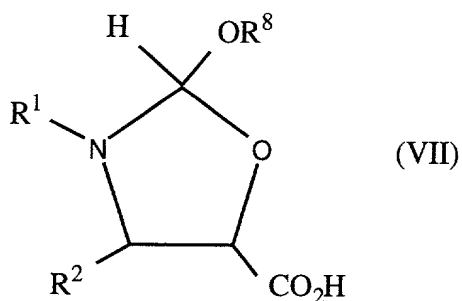
Compounds of the formula III include compounds of the formula I where R^4 is hydrogen. A compound of the formula I

15 where R^4 is other than hydrogen may be converted to a compound of the formula III where R^1 is R^{1*} by a novel method comprising the step of hydrolyzing said compound of the formula I where R^4 is other than hydrogen to form said compound of the formula III. Any compound capable of

20 effecting the hydrolysis may be employed as the hydrolyzing agent. Exemplary hydrolyzing agents include aqueous bases such as aqueous hydroxides (e.g., metal hydroxides such as barium hydroxide, or preferably, alkali metal hydroxides such as lithium, sodium or potassium hydroxide). Contact

25 with a base provides a carboxylic acid salt of a compound of the formula III. Further contact with an acid, preferably a mineral acid such as HCl, provides a compound of the formula

III where R^4 is hydrogen, that is, which contains a free carboxylic acid group. Compounds of the formula III where R^1 is other than R^{1*} may be prepared by methods analogous to those methods described herein for the preparation of

5   compounds of the formula III where R^1 is R^{1*}.

   In another embodiment of the invention, a compound of the formula VI or salt thereof may be prepared by a method comprising the steps of:

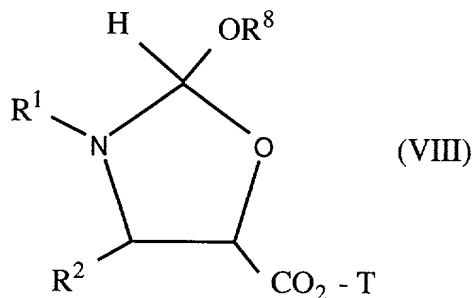   (a)   contacting a compound of the following
10   formula VII or salt thereof:

(VII)

with a compound of the following formula IV:

15

HO – T   (IV),

in the presence of a coupling agent, to form a compound of the following formula VIII or salt thereof:

20

(VIII)

where R^1, R^2, R^8 and T are as defined above; and

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(b)   contacting said compound of the formula VIII or salt thereof with a ring-opening agent to form said compound of the formula VI or salt thereof. Each of the steps (a) and (b) of this method are themselves novel

5   methods. Additionally, the compounds of the formulae VII and VIII and salts thereof are novel.

Compounds of the formula VII are compounds of the formula II where R^4 is hydrogen. A compound of the formula II where R^4 is other than hydrogen may be converted to a

10   compound of the formula VII by a novel method comprising the step of hydrolyzing said compound of the formula II where R^4 is other than hydrogen to form said compound of the formula VII. Hydrolysis of a compound of the formula II to form a compound of the formula VII may be conducted as described

15   above for the hydrolysis of a compound of the formula I where R^4 is other than hydrogen to form a compound of the formula III.

The ring of the present oxazolidine compounds is numbered herein as follows:

20
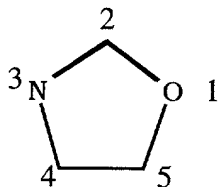
With respect to the 4- and 5-position carbon atoms, the oxazolidine compounds of the formulae I and II may exist as the four stereoisomers Ia or IIa, Ib or IIb, Ic or IIc

25   and Id or IId, respectively, as follows:

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(Ia)

(IIa)

(Ib)

(IIb)

(Ic)

(IIc)

5

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(Id)   (IId)
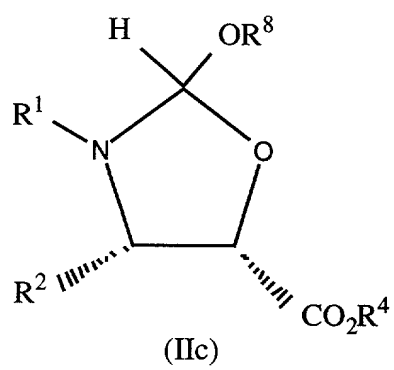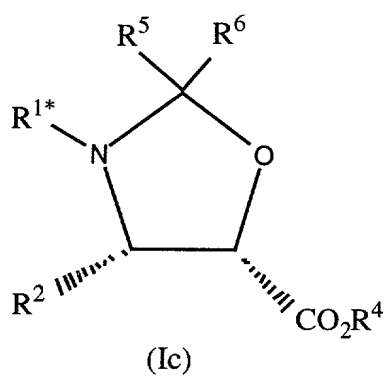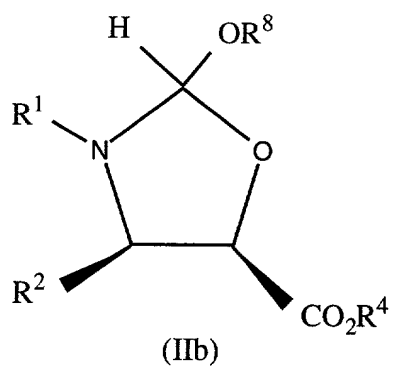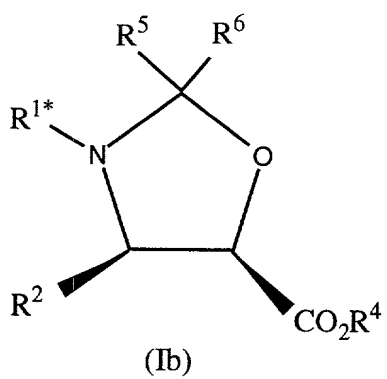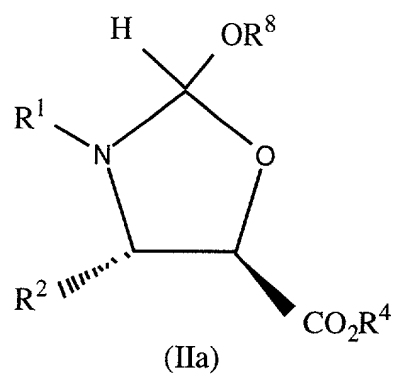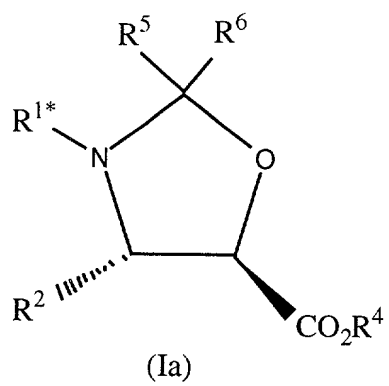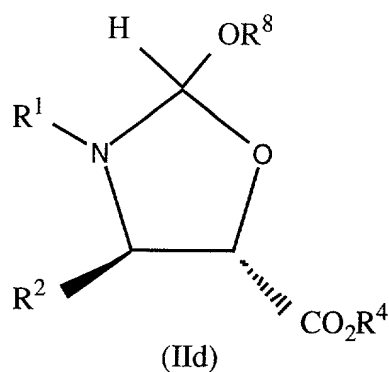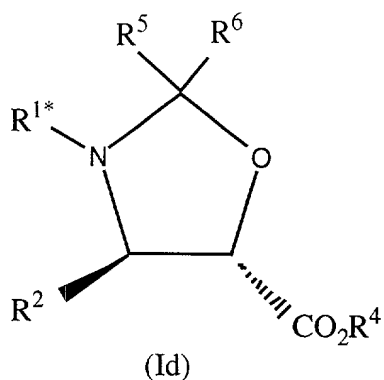
As the stereochemistry of taxanes may affect their pharmaceutical activity, it is desirable to employ oxazolidine intermediates which will provide the final

5   taxane product with the stereochemistry sought. While the use of stereoisomeric mixtures of a compound of the formula I or II is contemplated herein, the use of a single stereoisomer providing the desired stereochemistry in the final product may achieve a more efficient use of the

10 starting materials and less complicated separation and purification procedures.

Detailed Description of the Invention

The present invention is described further as

15 follows.

The terms "alkyl" or "alk", as used herein alone or as part of another group, denote optionally substituted, straight and branched chain saturated hydrocarbon groups, preferably having 1 to 12 carbons in the normal chain.

20 Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the like. Exemplary substituents may include one or more of the

25 following groups: halo, alkoxy, alkylthio, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (-COOH), alkyloxycarbonyl,

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alkylcarbonyloxy, carbamoyl (NH_2-CO-), amino (-NH_2), mono-
or dialkylamino, or thiol (-SH).

The terms "lower alk" or "lower alkyl", as used
herein, denote such optionally substituted groups as
described above for alkyl having 1 to 6 carbon atoms in the
normal chain.

The terms "alkoxy" or "alkylthio", as used herein,
denote an alkyl group as described above bonded through an
oxygen linkage (-O-) or a sulfur linkage (-S-),
respectively. The term "alkyloxycarbonyl", as used herein,
denotes an alkoxy group bonded through a carbonyl group.
The term "alkylcarbonyl", as used herein, denotes an alkyl
group bonded through a carbonyl group. The term
"alkylcarbonyloxy", as used herein, denotes an alkylcarbonyl
group which is bonded through an oxygen linkage. The terms
"monoalkylamino" or "dialkylamino" denote an amino group
substituted by one or two alkyl groups as described above,
respectively.

The term "alkenyl", as used herein alone or as part
of another group, denotes such optionally substituted groups
as described for alkyl, further containing at least one
carbon to carbon double bond. Exemplary substituents
include one or more alkyl groups as described above, and/or
one or more groups described above as alkyl substituents.

The term "alkynyl", as used herein alone or as part
of another group, denotes such optionally substituted groups
as described for alkyl, further containing at least one
carbon to carbon triple bond. Exemplary substituents
include one or more alkyl groups as described above, and/or
one or more groups described above as alkyl substituents.

The term "cycloalkyl", as used herein alone or as
part of another group, denotes optionally substituted,
saturated cyclic hydrocarbon ring systems, preferably
containing 1 to 3 rings and 3 to 7 carbons per ring.

Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include one or more alkyl groups as

5   described above, and/or one or more groups described above as alkyl substituents.

The term "cycloalkenyl", as used herein alone or as part of another group, denotes such optionally substituted groups as described above for cycloalkyl, further containing

10   at least one carbon to carbon double bond forming a partially unsaturated ring. Exemplary substituents include one or more alkyl groups as described above, and/or one or more groups described above as alkyl substituents.

The terms "ar" or "aryl", as used herein alone or as

15   part of another group, denote optionally substituted, homocyclic aromatic groups, preferably containing 1 or 2 rings and 6 to 12 ring carbons. Exemplary unsubstituted such groups include phenyl, biphenyl, and naphthyl. Exemplary substituents include one or more, preferably three

20   or fewer, nitro groups, alkyl groups as described above, and/or groups described above as alkyl substituents.

The term "arylcarbonyl", as used herein alone or as part of another group, denotes an aryl group as described above bonded through a carbonyl group.

25   The terms "heterocyclo" or "heterocyclic", as used herein alone or as part of another group, denote optionally substituted, fully saturated or unsaturated, aromatic or non-aromatic cyclic groups having at least one heteroatom in at least one ring, preferably monocyclic or bicyclic groups

30   having 5 or 6 atoms in each ring. The heterocyclo group may, for example, have 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring. Each heterocyclo group may be bonded through any carbon or heteroatom of the ring system. Exemplary heterocyclo groups

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include the following: thienyl, furyl, pyrrolyl, pyridyl, imidazolyl, pyrrolidinyl, piperidinyl, azepinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl,

5   benzofurazanyl, and especially, tetrahydropyranyl (e.g. 4-tetrahydropyranyl). Exemplary substituents include one or more alkyl groups as described above, and/or one or more groups described above as alkyl substituents.

The terms "halogen" or "halo", as used herein alone

10   or as part of another group, denote chlorine, bromine, fluorine, and iodine.

The term "taxane moiety", as used herein, denotes moieties containing the core structure:
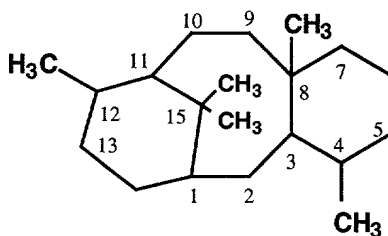
15   which core structure may be substituted and which may contain ethylenic unsaturation in the ring system thereof. Such moieties having an oxetane ring fused at the 4- and 5-positions, and an ethylenic double bond between C-11 and

20   C-12, such as are found in paclitaxel, are preferred.

The term "taxane", as used herein, denotes compounds containing a taxane moiety as described above. The term "C-13 acyloxy sidechain-bearing taxane", as used herein, denotes compounds containing a taxane moiety as described

25   above, further containing an acyloxy sidechain directly bonded to said moiety at C-13 through the oxygen of the oxy group of the acyloxy substituent.

The term "hydroxy (or hydroxyl) protecting group", as used herein, denotes any group capable of protecting a free

30   hydroxyl group which, subsequent to the reaction for which

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it is employed, may be removed without destroying the remainder of the molecule. Such groups, and the synthesis thereof, may be found in "Protective Groups in Organic Synthesis" by T.W. Greene, John Wiley and Sons, 1981, or

5 Fieser & Fieser. Exemplary hydroxyl protecting groups include methoxymethyl, 1-ethoxyethyl, 1-methoxy-1-methylethyl, benzyloxymethyl, (β-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-tri-chloroethoxycarbonyl, t-butyl(diphenyl)silyl, trialkylsilyl,

10 trichloromethoxycarbonyl, and 2,2,2-trichloroethoxymethyl.

     The term "salt", as used herein, includes salts with organic and/or inorganic acids and/or bases.

     The term "acyl", as used herein alone or as part of another group, denotes the moiety formed by removal of the

15 hydroxyl group from the group -COOH of an organic carboxylic acid. The term "acyloxy", as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (-O-).

13

<u>Preparation of Oxazolidines of the</u>
<u>Formulae I and II</u>

The oxazolidines of the formulae I and II and salts
thereof may be prepared starting with a compound of the
5   following formula i:
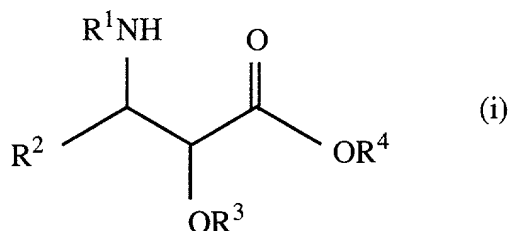
$$R^1NH \quad \overset{O}{\underset{R^2}{\overbrace{}}} \quad OR^4 \qquad \text{(i)}$$

$$OR^3$$

where R^1 is hydrogen, arylcarbonyl, alkoxycarbonyl or
10 alkylcarbonyl; R^2 is aryl, heterocyclo or alkyl; R^4 is
hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl,
cycloalkenyl or heterocyclo; and where R^3 is hydrogen or the
group R^{3P}, where R^{3P} is the group:

$$\begin{array}{c} R^5 \\ | \\ -C-R^6 \\ | \\ OR^7 \end{array}$$

15
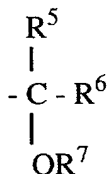
where R^5 and R^6 are as defined above, and R^7 is alkyl or
aryl. Compounds of the formula i may be prepared as
described in, or by methods analogous to those described in,
20 U.S. Application Serial No. 07/975,453, filed November 12,
1992 (Attorney Docket No. LD54), or U.S. Application Serial
No. 08/263,869, filed June 21, 1994 (Attorney Docket No.
LD68), or as described below.

Compounds of the formula I and salts thereof may be
25 prepared from compounds of the formula i and salts thereof
where R^1 is R^{1*} by a novel method comprising the step of

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contacting said compound of the formula i or salt thereof
with an acid catalyst, and additionally, where R^3 in said
compound of the formula i or salt thereof is hydrogen, with
a compound of the formula ii or iii described following.

5   The aforementioned compounds of the formulae ii and iii have
the following structures:

$$R^{5a} - CH = \overset{\displaystyle OR^7}{\underset{\displaystyle |}{C}} - R^6 \quad \text{(ii)}$$

$$\underset{R^7O \quad OR^7}{\overset{R^5 \quad R^6}{C}} \quad \text{(iii)}$$
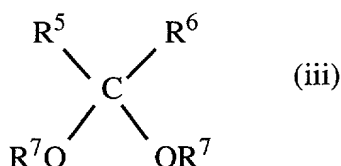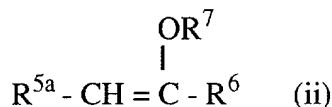
10

where R^5, R^6 and R^7 are as defined above, and where R^{5a} (i)
is a group such that $R^{5a}-CH_2-$ is R^5 or (ii) forms, together
with R^6 and the atoms to which R^{5a} and R^6 are bonded, a

15 cycloalkenyl or heterocyclo group containing at least one
carbon to carbon double bond. Compounds of the formulae ii
and iii are commercially available or may readily be
prepared by known methods. Exemplary compounds of the
formula ii include the compounds:

15
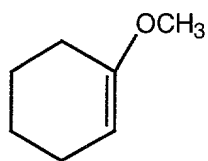
or
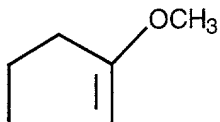
, or, most preferably, 2-methoxypropene.   Exemplary compounds of the formula iii include the compounds: dimethoxypropane,

5

or

.

Novel compounds of the following formula iv and salts thereof:

(iv)

10

where R^{1*}, R^2, R^{3P} and R^4 are as defined above may be formed as intermediates in the aforementioned method when a compound of the formula i or salt thereof in which R^3 is

15   hydrogen is contacted with the compound of the formula ii or iii.   In the presence of acid catalyst, the compound iv or salt thereof undergoes conversion to a compound of the formula I or salt thereof.

Compounds of the formula II and salts thereof may be

20   prepared from compounds of the formula i and salts thereof by a novel method comprising the step of contacting a compound of the formula i or salt thereof where R^3 is hydrogen, in the presence of an acid catalyst, with a compound of the following formula vi:

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$$HC(OR^8)_3 \qquad (vi)$$
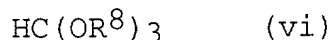
where R^8 is as defined above. Compounds of the formula vi

5 are commercially available or may readily be prepared by
known methods. Exemplary compounds of the formula vi
include trimethoxymethane and triethoxymethane.
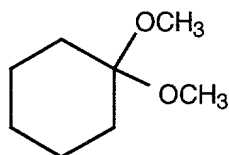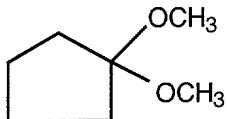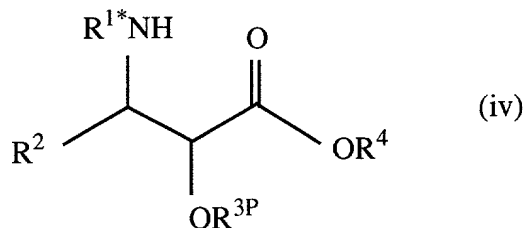
Novel compounds of the following formula v and salts
thereof:

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$$(v)$$
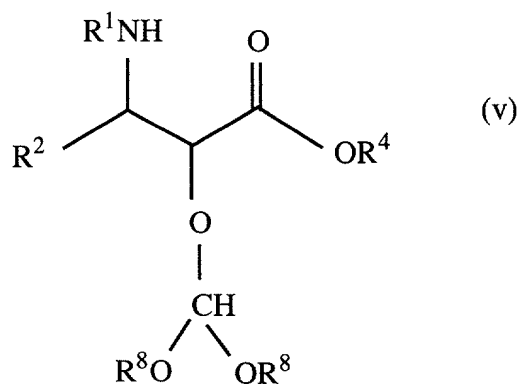
where R^1, R^2, R^4 and R^8 are as defined above may be formed
as intermediates in the aforementioned method. In the

15 presence of acid catalyst, the compound v or salt thereof
undergoes conversion to a compound of the formula II or salt
thereof.

For the conversion of a compound i to a compound I or
II as described above, the present methods employ an "acid

20 catalyst". Any acid catalyzing the method referred to may
suitably be employed as the acid catalyst, with organic
sulfonic acids (that is, organic acids containing the group
SO_2O^-) or sulfonates, or mineral acids being preferred.
Particularly preferred such acid catalysts include

25 pyridinium p-toluene sulfonate (PPTS), toluene sulfonic
acid, camphor sulfonic acid, and the like.

The compounds of the formula i and salts thereof may exist as four stereoisomers with respect to the carbon atoms at those positions corresponding to the 4- and 5-position carbon atoms of the compounds of the formulae I and II.

5   These stereoisomers are the following compounds of the formulae ia, ib, ic and id:

R^1NH

R^2 O

OR^4 (ia)

OR^3

R^1NH

R^2 O

OR^4 (ib)

OR^3

R^1NH

R^2 O

OR^4 (ic)

OR^3

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$$\text{(id)}$$
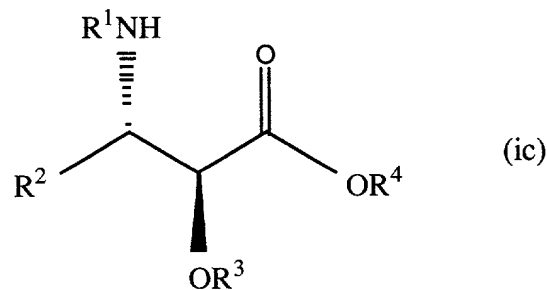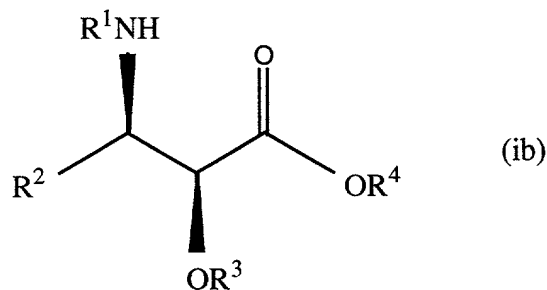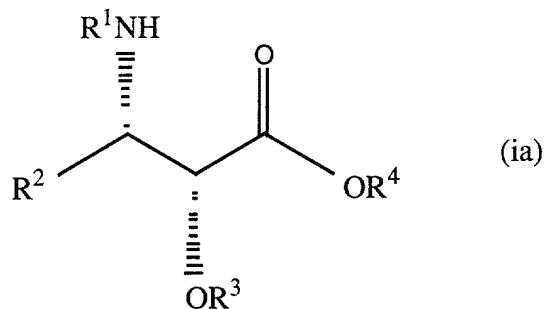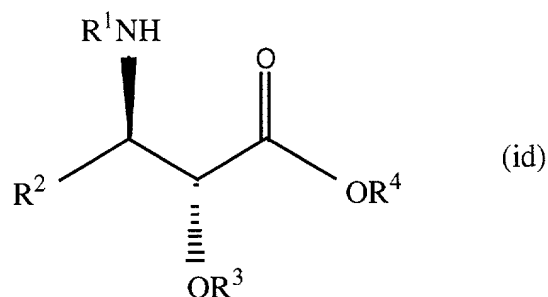
A desired stereoisomer of a compound of the formula I
or II or salt thereof may be prepared by the methods
5   described above by employing the appropriate stereoisomer of
the starting compound of the formula i or salt thereof.
Thus, use of a compound ia can provide a compound Ia or IIa,
use of a compound ib can provide a compound Id or IId, use
of a compound ic can provide a compound Ic or IIc, and use
10   of a compound id can provide a compound Ib or IIb. It is
preferred to employ a single stereoisomer of the starting
compound i or salt thereof in the above described methods,
although stereoisomeric mixtures may also be employed. Use
of a compound ia to prepare a compound Ia or IIa is
15   particularly preferred.

Coupling to Prepare Oxazolidine
Sidechain-bearing Taxanes

An oxazolidine sidechain-bearing taxane of the
20   formula V or VIII or salt thereof may be prepared by a
method comprising the step of contacting an oxazolidine
compound of the formula III or VII, respectively, or salt
thereof, in the presence of a coupling agent, with a taxane
of the formula IV having a hydroxyl group directly bonded to
25   C-13 thereof. The taxane starting material of the formula
IV is preferably a compound such as those described in
European Patent Publication No. 400,971, incorporated herein
by reference, or a compound such as those described in U.S.
Patent Application Serial No. 08/995,443, filed December 23,

1992 by Poss et al., or continuation-in-part thereof U.S.
Patent Application Serial No. 08/171,792, filed December 22,
1993, both also incorporated herein by reference. Exemplary
such taxanes include those of the following formula IX:

5

$$\text{(IX)}$$
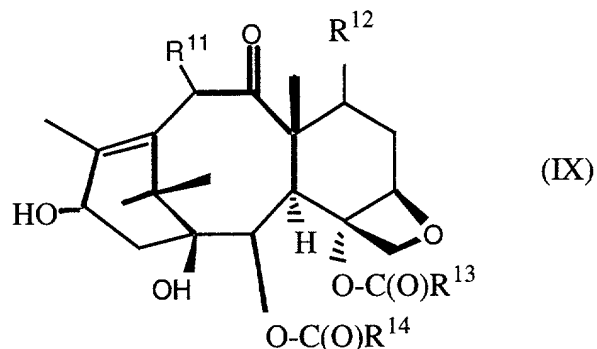
where

R^{11} is hydrogen, hydroxyl, R^{15}-O-, R^{16}-C(O)-O-, or

10 R^{16}-O-C(O)-O-;

R^{12} is hydrogen, hydroxyl, fluoro, R^{15}-O-,

R^{16}-C(O)-O- or R^{16}-O-C(O)-O-;

R^{13} and R^{14} are independently hydrogen, alkyl, alkenyl,

alkynyl, cycloalkyl, cycloalkenyl, aryl, or

15 heterocyclo;

R^{15} is a hydroxyl protecting group; and

R^{16} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,

cycloalkenyl, aryl or heterocyclo,

or salts thereof.

20 All stereoconfigurations of the unspecified chiral
centers of the compound of the formula IX are contemplated
for use in the coupling method of the present invention.
The use of a single stereoisomer is preferred, although
mixtures thereof may be employed. 7-Trialkylsilyl baccatin

25 III compounds are preferably employed as the compounds of

the formula IV, most preferably, 7-trimethylsilyl baccatin III or 7-triethylsilyl baccatin III.

Any compound capable of effecting the coupling reaction may be employed as the coupling agent of the

5   present invention. Exemplary coupling agents include one or more compounds forming an activated oxazolidine ester (for example, 1-hydroxybenzotriazole or N-hydroxysuccinimide, both of these with dicyclohexylcarbodiimide (DCC)) or anhydride (for example, an acid chloride such as pivaloyl

10 chloride or bis(2-oxo-3-oxazolidinyl)-phosphinic chloride) when contacted with an oxazolidine of the formula III or VII, particularly coupling agents comprising a compound such as a carbodiimide (e.g., dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide (DIC), or 1-(3-dimethyl-

15 aminopropyl)-3-ethyl-carbodiimide hydrochloride), bis(2-oxo-3-oxazolidinyl)phosphinic chloride), carbonyl diimidazole (CDI), pivaloyl chloride, or 2,4,6-trichlorobenzoyl chloride; wherein the aforementioned compounds are preferably employed together with a compound such as

20 1-hydroxybenzotriazole (HOBt) or N-hydroxysuccinimide (HO-Su), or an amine such as triethylamine, pyridine or pyridine substituted at the 4-position with -N(R^{17})(R^{18}), where R^{17} and R^{18} are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or heterocyclo (to form a

25 compound such as 4-dimethylaminopyridine (DMAP)), or where R^{17} and R^{18}, together with the nitrogen atom to which they are bonded, form a heterocyclo group (to form a compound such as 4-morpholinopyridine or 4-pyrrolidinopyridine).

21

Ring Opening to Form Taxanes of the
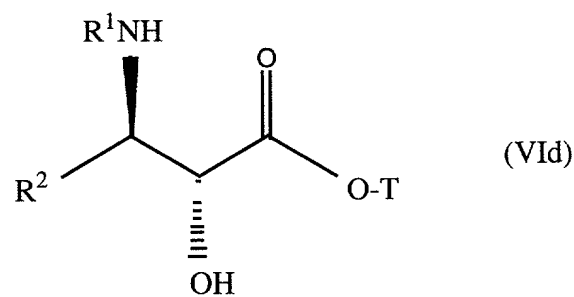### Formula VI

A sidechain-bearing taxane of the formula VI or salt thereof may be prepared from an oxazolidine sidechain-

5   bearing taxane of the formula V or VIII or salt thereof, by a method comprising the step of contacting said taxane of the formula V or VIII or salt thereof with a ring-opening agent capable of opening the ring of the oxazolidine group bonded through C-13 of the taxane moiety of said taxane

10 compound to form said taxane compound of the formula VI or salt thereof.

A preferred class of ring-opening agents for the conversion of a compound V or salt thereof to a compound VI or salt thereof are Lewis acids which preferably cause

15 minimal or, most preferably, no decomposition of the compounds V or VI or salts thereof ("mild Lewis acids"). Any Lewis acid capable of effecting the aforementioned ring opening may be employed in the method of the present invention. Exemplary such agents include palladium

20 containing agents such as $Pd(CH_3CN)_2Cl_2$.

A preferred class of ring-opening agents for the conversion of a compound VIII or salt thereof to a compound VI or salt thereof are protic acids. Any protic acid capable of effecting the aforementioned ring opening may be

25 employed in the method of the present invention. Exemplary such ring-opening acids include organic carboxylic acids, such as acetic acid or trifluoroacetic acid, and/or mineral acids such as hydrochloric acid, hydrofluoric acid or sulfuric acid, in water.

30 The compounds of the formula VI and salts thereof may exist as four stereoisomers with respect to the carbon atoms at those positions corresponding to the 4- and 5-position carbon atoms of the compounds of the formulae I and II.

These stereoisomers are the following compounds of the
formulae VIa, VIb, VIc and VId:

$$R^1NH$$

(VIa)

5

$$R^1NH$$

(VIb)

$$R^1NH$$

(VIc)

$$R^1NH$$

(VId)

10

23
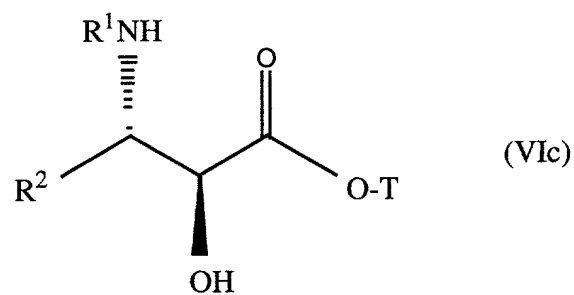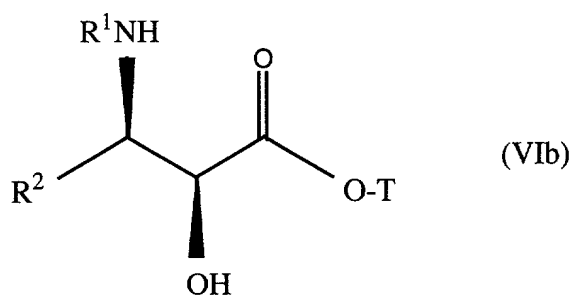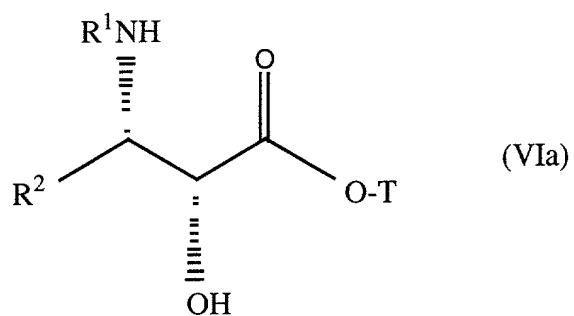
A desired stereoisomer of the compound of the formula VI or salt thereof may be prepared by the methods described above by employing the appropriate stereoisomer of the starting compound of the formula III or VII or salt thereof. Using the designations "a" through "d" to refer to the stereoisomers of the formulae III and VII as are used for the compounds I and II above: use of a compound IIIa or VIIa will provide a compound VIa; use of a compound IIId or VIId will provide a compound VIb; use of a compound IIIc or VIIc will provide, predominantly, a compound VIa along with a minor amount of a compound VIc; and use of a compound IIIb or VIIb will provide, predominantly, a compound VIb along with a minor amount of a compound VId. It is preferred to employ a single stereoisomer of the starting compound III or VII or salt thereof in the above described methods, although stereoisomeric mixtures may also be employed. Use of a compound Ia to prepare a compound VIa is particularly preferred.

A preferred embodiment of the present invention further comprises the step of deprotecting one or more groups, particularly to free hydroxyl groups, on the taxane moiety to prepare taxanes of the formula VI or salts thereof. Deprotection may, for example, be conducted prior or subsequent to, or simultaneously with, the aforementioned ring opening methods by use of a deprotection agent. Any compound capable of deprotection may be employed as the deprotection agent. For example, acids such as hydrofluoric acid or aqueous protic acids, or tetra-alkylammonium fluorides such as tetra-n-butylammonium fluoride, may be employed for removal of silyl protecting groups; benzyl protecting groups may be removed by hydrogenation; trichloroethoxycarbonyl protecting groups may be removed by contact with zinc; and acetal or ketal protecting groups may be removed by the use of protic acids or Lewis acids.

24

A particularly preferred embodiment of the present invention comprises simultaneous ring opening and deprotection of one or more hydroxyl groups on the taxane ring structure, particularly at C-7, such as by the use of

5 an acid (e.g., a mineral acid such as hydrochloric acid) capable of effecting both ring opening and deprotection simultaneously. Thus, for example, use of an acid agent under reaction conditions described above for ring opening may allow simultaneous ring opening and deprotection of

10 cleavable hydroxyl protecting groups at C-7 such as trialkylsilyl (e.g. trimethylsilyl or triethylsilyl).

Preferred Reaction Conditions

The methods of the present invention may be conducted

15 under any conditions, such as temperature, pressure and time, and using the appropriate starting materials and catalysts in any relative amount, effective to achieve the desired conversion. Similarly, a solvent may be employed if desired and may be selected from any material in which the

20 conversion may be conducted, including inorganic (e.g., aqueous) or organic (e.g., acetone, dimethylformamide, tetrahydrofuran, methylene chloride, acetonitrile, benzene or toluene) liquids or mixtures thereof. Solvents are preferably employed which are inert to the reaction.

25 The products of the methods of the present invention may be isolated and purified by any suitable methodology such as extraction, distillation, crystallization, column chromatography, and the like.

Particularly preferred reaction conditions for

30 conducting various methods described herein are set forth in the following Tables 1 to 6.

Salts or solvates such as hydrates of reactants or products may be employed or prepared as appropriate in any of the methods of the present invention. Unless otherwise

25

indicated, reference to a compound herein is understood to include salts and/or solvents thereof.

Table 1

Preferred Reaction Conditions for the Preparation of a
Compound of the Formula I

starting compounds	i; and ii or iii when R^3 = H in i
molar ratio of ii or iii:i	molar excess of ii or iii:i
catalyst	acid catalyst
molar ratio of catalyst:i	0.03:1 to 0.1:1
temperature (°C)	80 to 110
pressure (atm)	atmospheric
atmosphere	gas inert to reaction
solvent	organic
amount of solvent (weight of i: volume of solvent)	1 g:50 ml to 1 g:100 ml

5

    Compound iv can be formed as an intermediate and
converted to a compound of the formula I *in situ* due to the
presence of acid catalyst, or contacted with acid catalyst
in a separate step.

10

Table 2

Preferred Reaction Conditions for the Preparation of a
Compound of the Formula II

starting compound	i (R^3 = H) and vi
molar ratio of vi:i	molar excess of vi:i
catalyst	acid catalyst
molar ratio of catalyst:i	0.03:1 to 0.1:1
temperature (°C)	80 to 110
pressure (atm)	atmospheric
atmosphere	gas inert to reaction
solvent	organic
amount of solvent (weight of i:volume of solvent)	1 g:50 ml to 1 g:100 ml

5

Compound v can be formed as an intermediate and
converted to a compound of the formula II.

Table 3

Preferred Reaction Conditions for the Preparation of a

Compound of the Formula III or VII

starting compound	I or II (where R^4 • H); and base
molar ratio of base:I or II	1:1 to 1.05:1
further starting material	acid
molar ratio of acid:I or II	1:1 to 1.05:1
temperature (°C)	room (~25°C)
pressure (atm)	atmospheric
atmosphere	gas inert to reaction
solvent	aqueous/organic mixture
amount of solvent (weight of I or II: volume of solvent)	1 g:50 ml to 1 g:100 ml

5

As described above, use of the base only can provide a formula III or VII salt; further use of an acid provides the free carboxylic acid.

29

Table 4
Preferred Reaction Conditions for the Preparation of a
Compound of the Formula V or VIII

starting compound	III or VII; and IV
molar ratio of III or VII:IV	molar excess of III or VII:IV, especially molar ratio of 1.1:1 to 1.5:1
coupling agent	carbodiimide or phosphinic chloride and amine
molar ratio of carbodiimide or phosphinic chloride:III or VII	1.5:1 to 1:1
molar ratio of amine:III or VII	0.5:1 to 1:1
temperature (°C)	60 to 100
pressure (atm)	atmospheric
atmosphere	gas inert to reaction
solvent	organic
amount of solvent (weight of III or VII: volume of solvent)	1 g:5 ml to 1 g:10 ml

5

Table 5

Preferred Reaction Conditions for the Preparation of a
Compound of the Formula VI Using Protic Acid

starting compound	VIII; and protic acid (especially, aqueous protic acid)
molar ratio of acid:VIII	molar excess of acid:VIII
temperature (°C)	0 to 25
pressure (atm)	atmospheric
atmosphere	gas inert to reaction
solvent	aqueous/organic
amount of solvent (weight of VIII: volume of solvent)	1 g:10 ml to 1 g:20 ml

5

Table 6

Preferred Reaction Conditions for the Preparation of a
Compound of the Formula VI Using Lewis acid

starting compound	V; and Lewis acid (especially, mild Lewis acid)
molar ratio of Lewis acid:V	0.02:1 to 0.1:1
temperature (°C)	room (~25°C)
pressure (atm)	atmospheric
atmosphere	gas inert to reaction
solvent	organic
amount of solvent (weight of V: volume of solvent)	1 g:5 ml to 1 g:15 ml

5

Preferred Groups

Preferred groups forming part of compounds used or
10 prepared by the present invention are those where:

R^1 and R^{1*} are each independently arylcarbonyl
(especially benzoyl) or alkyloxycarbonyl (especially
unsubstituted lower alkyloxycarbonyl such as tert-
butoxycarbonyl);

15 R^2 is phenyl, thienyl or furyl;

R^3 is hydrogen or R^{3P} where R^5, R^6 and R^7 are each
independently unsubstituted lower alkyl (especially, methyl
or ethyl);

R^4 is hydrogen or unsubstituted lower alkyl
20 (especially, methyl or ethyl);

32

R^5, R^6 and R^7 are each independently unsubstituted lower alkyl (especially, methyl or ethyl);

R^8 is unsubstituted lower alkyl (especially methyl or ethyl); and

5   T is the moiety:
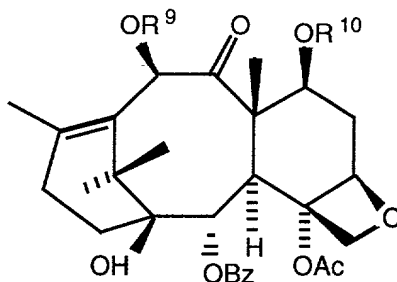
where

R^9 is hydrogen, alkylcarbonyl, or a hydroxyl protecting
10   group, especially acetyl; and
R^{10} is hydrogen or a hydroxyl protecting group, especially a
trialkylsilyl group such as triethylsilyl or trimethylsilyl.

C-13 Acyloxy Sidechain-bearing Taxanes

15   The addition of a C-13 acyloxy sidechain as described
herein, in and of itself, may impart an increased or more
desirable pharmacological activity to the taxane product, or
may form a taxane product which is more readily converted to
a taxane having an increased or more desirable
20   pharmacological activity than the starting compound.
Exemplary taxanes which may be prepared by the present
methods for the preparation of sidechain-bearing taxanes
include those taxanes described in European Patent
Publication No. 400,971, and U.S. Patent Applications
25   07/995,443, filed December 23, 1992 and 08/171,792, filed
December 22, 1993, all incorporated herein by reference. It
is preferred to ultimately prepare taxotere or, most
preferably, paclitaxel according to the methods of the
present invention.

Pharmacologically active taxanes such as paclitaxel may be used as antitumor agents to treat patients suffering from cancers such as breast, ovarian, colon or lung cancers, melanoma and leukemia.

5   As can be appreciated, the oxazolidines, taxanes and other compounds described herein may be present in more than one stereoisomeric form. All stereoisomers of the compounds described herein are contemplated, whether alone (that is, substantially free of other isomers), in admixture with

10   certain stereoisomers (for example, as a racemate) or in any other mixture thereof. It is preferred that these compounds be substantially free of other stereoisomers.

The present invention is further described by the following examples which are illustrative only, and are in

15   no way intended to limit the scope of the present claims.

Abbreviations

The following abbreviations have the indicated meaning throughout the present specification.

5

Ac = acetyl

Bz = -C(O)-Ph (i.e., benzoyl)

DCC = dicyclohexylcarbodiimide

DMAP = dimethylaminopyridine

10   DMF = dimethylformamide

Et = ethyl

EtOAc = ethyl acetate

MOP = 1-methoxy-1-methylethyl

Ph = phenyl

15   HI = homogeneity index

PMA = phosphomolybdic acid

PPTS = pyridinium p-toluene sulfonate

TEA = triethylamine

TES = triethylsilyl
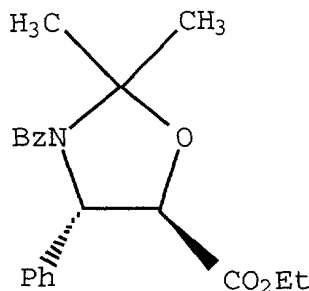
20   THF = tetrahydrofuran

TLC = thin layer chromatography

The following Examples 1 to 4 demonstrate cyclizations forming a preferred oxazolidine ester compound of the formula I or II of the present invention.

5

EXAMPLE 1

Preparation of (4S-trans)-3-Benzoyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid, ethyl ester

10

[R-(R*,S*)]-β-(Benzoylamino)-α-hydroxybenzenepropanoic acid, ethyl ester:
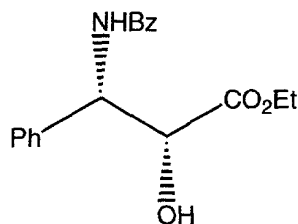
15 (225 mg, 0.7183 mmol) was suspended in methylene chloride (CH2Cl2, 3.0 ml), and DMF (2.0 ml) was added until a clear solution resulted. The mixture was cooled to 0°C, and 2-methoxypropene (1.7957 mmol) was added, followed by PPTS (approximately 5 mg, 0.016 mmol). The mixture was stirred

20 for 4 hours, then another 2.6 eq. (1.7957 mmol) of 2-methoxypropene were added. The addition was repeated twice more at intervals of 2 hours, and the mixture was allowed to stand overnight at room temperature. The reaction was quenched with saturated NaHCO3, and the mixture was washed

36

with saturated NaHCO$_3$, dried, and the solvent removed to give the product in quantitative yield. The residue was refluxed in an excess of toluene and 2,2-dimethoxypropane and azeotroped overnight. HPLC isolation gave 73 mg of the

5   title product (29%).

TLC (hexanes/ethyl acetate = 2:1) Rf = 0.48

m.p. = 87-88 C

^{1}H NMR in accordance with the above structure.

10   EXAMPLE 2

Alternative Preparations (A) and (B) of (4*S*-*trans*)-3-Benzoyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid, ethyl ester

15   (A)   [*R*-(*R**,*S**)]-β-(Benzoylamino)-α-hydroxybenzenepropanoic acid, ethyl ester (2.200 mg) was suspended in toluene (250 ml) and the flask equipped with a Dean-Stark trap. After heating to reflux, the compound dissolved. 40 ml of toluene were distilled off, PPTS (120

20   mg) and 2-methoxypropene (3.5 ml) were added, and distillation was continued. Further additions of 2-methoxypropene (2 ml, and then 1 ml) and toluene (50 ml, and then another 50 ml) were made, and the distillate periodically discarded. Purification on HPLC (hexane/ethyl

25   acetate, 3:1) gave 2.3 g (93%) of the title product in a mixture with other reaction products. (Product characteristics consistent with structure of Example 1.)

         (B)   [*R*-(*R**,*S**)]-β-(Benzoylamino)-α-(1-methoxy-1-

30   methylethoxy)benzenepropanoic acid, ethyl ester:

NHBz

Ph

CO₂Et

OMOP
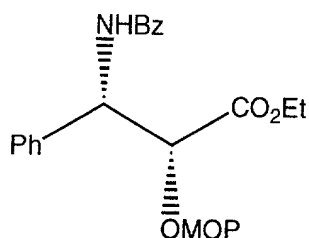
(2.200 mg) was mixed with toluene (200 ml) and PPTS (75 mg)
was added. The mixture was heated and toluene removed in a
Dean-Stark trap. After 70 ml of toluene were removed, a TLC
was conducted which showed a mixture of products and the
hydroxyester starting material of Example 1. 2-
Methoxypropene (0.5 ml) was added and the distillation
continued. A second charge of 2-methoxypropene (0.5 ml) was
added and the distillation continued. When the volume
dropped to about 70 ml, TLC showed only the title product.
It was purified by HPLC (hexanes/ethyl acetate, 5:1 to 1:1)
to give 1.56 mg of the title product (75% overall yield from
the starting compound) in admixture with other reaction
products. (Product characteristics consistent with
structure of Example 1.)

EXAMPLE 3

Preparation of (4S,5R)-3-Benzoyl-2-ethoxy-4-phenyl-5-oxazolidinecarboxylic acid, ethyl ester

5
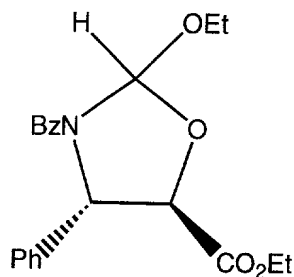
[R-(R*,S*)]-β-(Benzoylamino)-α-

10   hydroxybenzenepropanoic acid, ethyl ester (1.16 mmol) is
suspended in benzene (10 ml), and triethoxymethane (3.44
mmol) and PPTS (72 mg) are added. Heating to reflux
provides the title compound.

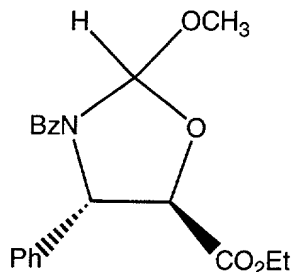## EXAMPLE 4

Preparation of (4S,5R)-3-Benzoyl-2-methoxy-4-phenyl-5-oxazolidinecarboxylic acid, ethyl ester

5

(A) [R-(R*,S*)]-β-(Benzoylamino)-α-
hydroxybenzenepropanoic acid, ethyl ester (1.16 mmol) was
10 suspended in benzene (10 ml), and trimethoxymethane (3.44
mmol) and PPTS (72 mg) were added. Heating to reflux
(103°C) did not dissolve the starting compound. 2 ml of DMF
were then added so that most of the starting compound
dissolved, although the solution remained somewhat turbid.
15 The flask was equipped with a Soxhlet extractor. The
thimble of the extractor was filled with 4Å mol. sieves.
After 1 hour, and approximately 3 to 4 cycles in the Soxhlet
extractor, TLC showed consumption of the starting material,
and a new major spot of the title product. It was diluted
20 with EtOAc, washed with $NaHCO_3$ and H_2O, dried and the
solvent removed. NMR showed the presence of the title
product and a small impurity. The product was purified on
HPLC (hexane:ethyl acetate, 3:1) to give 358 mg (87%) of the
title product.

40

(B) Preparation of the title compound was conducted on a larger scale as follows. [R-(R*,S*)]-β-(Benzoylamino)-α-hydroxybenzenepropanoic acid, ethyl ester (3.138 g) was

5 suspended in benzene (100 ml), and trimethoxymethane (3.190 g) and PPTS (628 mg) were added. The reaction solution was heated to reflux, 20 ml of DMF were added for dissolution of most of the starting compound, followed by heating with a Soxhlet extractor. The thimble in the extractor was filled

10 with 4Å mol. sieves. After 1 hour, and approximately 3 to 4 cycles in the Soxhlet extractor, TLC showed consumption of the starting material, and a new major spot of the title product. It was diluted with EtOAc, washed with NaHCO3 and H2O, dried and the solvent removed. NMR showed the presence

15 of the title product and a small impurity. The product was purified on HPLC (hexane:ethyl acetate, 3:1) to give 3.138 g (97%) of the title product. The product (an oil) was a mixture of diastereomers (not separated).

Mass spec.: $M+H^+$ = 356

20 TLC (hexanes/ethyl acetate = 2:1) Rf = 0.41

^{1}H NMR in accordance with the above structure.

The following Examples 5 to 7 demonstrate hydrolysis of the ester group of a preferred oxazolidine ester of the

25 formula I or II to form the corresponding carboxylic acid, or salt thereof, of the formula III or VII.

41

EXAMPLE 5

Preparation of (4S-trans)-3-Benzoyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid, lithium salt

5
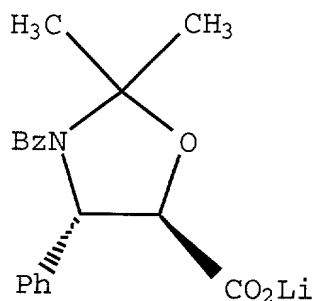
(4S-trans)-3-Benzoyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid, ethyl ester (73 mg) was

10 dissolved in THF (0.5 ml) at room temperature and LiOH (0.217 ml, 1M in H_2O) was added dropwise. Initially, a bi-phasic mixture was observed, but after the addition of the last quantity of LiOH and stirring for 5 minutes the solution became homogeneous. After further stirring for 1/2

15 hour, the solvents were removed *in vacuo*. The residue was azeotroped with toluene/methanol and dried at 55°C overnight under high vacuum. The title lithium salt was obtained (no further purification).

EXAMPLE 6

Preparation of (4*S-trans*)-3-Benzoyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid
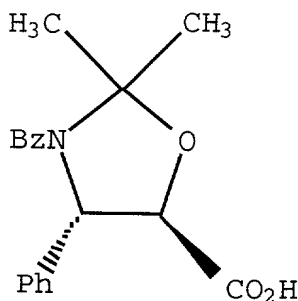
5

(4*S-trans*)-3-Benzoyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid, ethyl ester (1.56 g) was

10 dissolved in THF (10 ml) at room temperature and LiOH (4.63 ml, 1M in H_2O) was added dropwise. Initially, a bi-phasic mixture was observed, but after the addition of the last quantity of LiOH and stirring for 5 minutes the solution became homogeneous. After further stirring for 1/2 hour,

15 the reaction mixture was quenched with aqueous 1N HCl (4.63 ml), and diluted with EtOAc and saturated NaCl. The H_2O layer (pH = 3) was twice extracted with EtOAc, and the combined organic phase dried with $MgSO_4$. The solvent was removed *in vacuo* to give 1.39 g of the title product acid

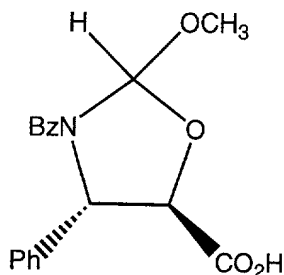20 (97%) which was homogeneous by TLC and ^{1}H NMR.
TLC (ethyl acetate/acetone/methanol/water = 7:1:1:1)
        Rf = 0.40
m.p. = 173-176°C

^{1}H NMR in accordance with the above structure.

25

43

EXAMPLE 7

Preparation of (4S,5β)-3-Benzoyl-2-methoxy-4-phenyl-5-oxazolidinecarboxylic acid

5

A procedure analogous to that of Example 6 was
employed, substituting the title product of Example 4 (177
10   mg) in place of the title product of Example 1 and employing
the following amounts of the remaining reagents: 0.524 ml 1N
LiOH, 2.0 ml THF and 0.524 1N HCl.   161 mg of the crude
title product (99%) was obtained.   The same procedure was
carried out at a larger scale (using 3,580 mg of the title
15   product of Example 4, 10.38 ml of 1N LiOH, 40 ml of THF, and
10.38 ml of 1N HCl) to yield 3.23 g of the crude title
product (98%) (minor impurity present).   The product was a
mixture of diastereomers (not separated).
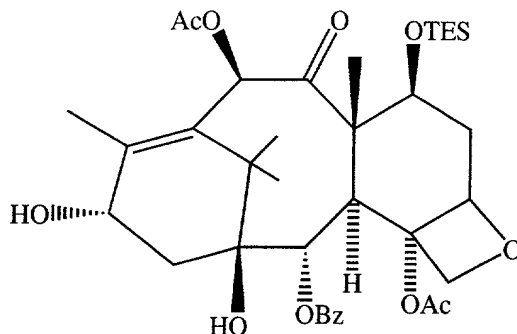TLC (ethyl acetate/acetone/methanol/water = 7:1:1:1)
20   Rf = 0.35

m.p. (mixture) = 160-162°C

^{1}H NMR in accordance with the above structure.

The following Example 8 demonstrates the preparation
25   of a preferred starting C-13 hydroxyl-bearing taxane
material of the formula IV.

EXAMPLE 8

Preparation of 7-Triethylsilylbaccatin III

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(i)   [2aR-(2aα,4β,6β,9α,11β,12α,12aα,12bα)]-
     Benzoic acid, 12b-acetyloxy-2a,3,4,4a,5,-
     6,9,10,11,12,12a,12b-dodecahydro-6,9,11-
     trihydroxy-4a,8,13,13-tetramethyl-5-oxo-
     4-[(triethylsilyl)oxy]-7,11-methano-1H-
     cyclodeca[3,4]benz[1,2-b]oxet-12-yl ester
     (7-O-TES-10-Desacetylbaccatin III)
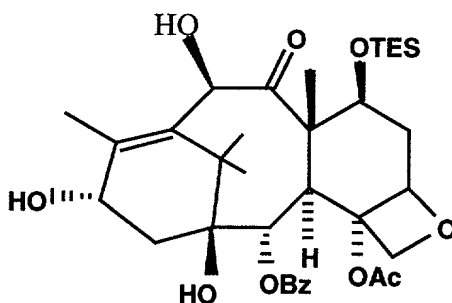
10-Desacetylbaccatin III (27.4 g, 50.3 mmol) (amount
not corrected for impurities measured (twice) as: H_2O: 1.0%
(1.57%), CH_3OH: 1.49% (1.6%), ethyl acetate: 0.1% (0.09%),
hexane (0.03%)) and 4-dimethylaminopyridine (2.62 g, 21.4
mmol) (wt. % H_2O (K.F.) = 0.09) were added to a flame-dried,
argon purged 1 L 3-necked flask (equipped with a mechanical
stirrer and a digital thermometer) and were dissolved in dry
dimethylformamide (122 ml) (wt. % H_2O (K.F.) = <0.01).
CH_2Cl_2 (256 ml) (wt. % H_2O (K.F.) = <0.01) was added and the

resulting homogeneous solution was cooled to -50°C. (The temperature of the reaction solution rose from 23°C to 25°C during the addition of CH_2Cl_2.) Triethylamine (NEt_3, 16 ml,
120 mmol) (wt. % H_2O (K.F.) = 0.08) was added dropwise over
5   3 minutes and the resulting solution was stirred at -50°C for 5 minutes before the dropwise addition of neat triethylsilyl chloride (Et_3SiCl, 18.6 ml, 111 mmol). The addition of Et_3SiCl was conducted over a period of 10 minutes and the temperature of the reaction did not rise
10 above -50°C. The reaction became very cloudy during the addition of Et_3SiCl. The resulting mixture was stirred at ~-50°C for 1 hour and was then allowed to stand (without stirring) in a -48°C freezer for 22 hours. (A separate experiment showed that stirring the reaction at -48°C for 8
15 hours resulted in ~60% conversion.) The mixture was then removed from the freezer and warmed to ~-10°C. (TLC analysis of the mixture (solvent: ethyl acetate, stain: phosphomolybdic acid/ethanol) revealed the absence of starting material and showed a single spot for the product
20 (Rf = 0.60).) The cold mixture was combined with EtOAc (1L) and washed with H_2O (890 ml). The resulting aqueous layer was separated and extracted with EtOAc (250 ml). The combined organic layers were washed with 5.7% aqueous NaH_2PO_4 (2 x 250 ml) (measured pH of 5.7% aqueous NaH_2PO_4 =
25 4.30 ± 0.05; measured pH of the combined NaH_2PH_4 washings = 5.75 ± 0.05), half-saturated aqueous NaCl (250 ml), saturated aqueous NaCl (250 ml), dried over Na_2SO_4, filtered and concentrated on a rotovap. (All concentrations on the rotovap were conducted with a water bath temperature of
30 35°C.) The resulting semi-solid was further dried by exposure to high vacuum (~1 mm Hg for 20 minutes) to give 41.5 g of a white solid. The crude product was then dissolved in CH_2Cl_2 (400 ml) (heating in a 35°C water bath

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was required to dissolve the solid) and the volume of the resulting solution was reduced to ~150 ml on a rotovap. Crystallization started immediately and the mixture was allowed to stand at room temperature for 1 hour. Hexanes (100 ml) were added and the mixture was gently swirled. The mixture was allowed to stand in a 4°C cold room for 16.5 hours. The solid was filtered, washed with 1:9 CH_2Cl_2/hexanes (3 x 250 ml) on a suction filter, and dried under high vacuum (~0.2 mm Hg for 42 hours) to give 26.1 g (79%) of the title product as a white powder. The mother liquor was concentrated on a rotovap and the residue was crystallized from CH_2Cl_2 to give 4.5 g (14%) of the title product as white crystals. Recrystallization was conducted in the same manner as with the first crop of product: the solid was dissolved in CH_2Cl_2 (100 ml) without heating and the volume of the resulting solution was reduced to ~7 ml on a rotovap. Crystallization began within 5 minutes. The mixture was allowed to stand at room temperature for 1 hour, then in a 4°C cold room for 42 hours. The crystals were filtered, washed with 1:9 CH_2Cl_2/hexanes (3 x 50 ml) on a suction filter, and dried under high vacuum (~0.2 mm Hg for 18 hours.). The ^{1}H NMR of this crop was identical to the ^{1}H NMR of the first crop of product.

The combined yield for the two crops was 93% (uncorrected).

Elemental Analysis (%)

$C_{35}H_{50}O_{10}Si$
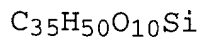
	Calcd.	Found
C	63.80	63.43
H	7.65	7.66
KF(H_2O)	0.00	0.00

mp: 239 - 242°C (decomp.)

$[\alpha]^{22}_D$: -53.6° (c 1.0, $CHCl_3$)

TLC: R_f = 0.60 (silica gel, EtOAc); visualized by phosphomolybdic acid/ethanol.

An alternative procedure was employed as follows:

In a flame-dried 250 ml 3-necked flask equipped with
5   an argon inlet was placed 10-des-
acetylbaccatin III (5.44 g, 10 mmol, having a water content
of 1.56 wt. % and a methanol content of 1.6 wt %),
4-dimethylaminopyridine (0.49 g, 4 mmol) and
N,N-dimethylformamide (24 ml, dried over 4Å molecular
10 sieve). The mixture was stirred at room temperature until
homogeneous. Dichloromethane (50 ml, HPLC grade, used
without purification) was added and the temperature was
lowered to -50°C. Triethylamine (2.9 ml, 21 mmol) was added
dropwise over a 5 minute period, followed by
15 triethylsilylchloride (3.4 ml, 20 mmol) over a 10 minute
period. The mixture was allowed to stand at -48°C for a
period of 21 hours, diluted with 200 ml of ethyl acetate and
175 ml of water. (The reaction was monitored by TLC using
EtOAc as eluent: R_f for the starting material = 0.56, R_f for
20 the product = 0.83; UV and PMA visualization.) The aqueous
layer was separated and extracted with ethyl acetate (50 ml
x 1). The organic layers were combined and washed with 5%
aqueous potassium phosphate mono basic (50 ml x 2) (pH of 5%
KH_2PO_4 in H_2O was 4.3), half-saturated sodium chloride (50
25 ml x 1), brine (50 ml x 1), dried over sodium sulfate and
concentrated *in vacuo* to give crude title product as a solid
(7.45 g). The crude material was dissolved in 75 ml of hot
dichloromethane and the total volume was reduced to 30 ml by
heating to begin crystallization. It was set aside at room
30 temperature for 2 hours and 4°C for 16 hours. The crystals
were filtered on a buchner funnel, washed with cold 10%
dichloromethane in hexane (25 ml) and dried *in vacuo* to
afford 5.38 g of title product. The mother liquors and
washings were concentrated *in vacuo* and the solid residue

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was crystallized by dissolving in 8 ml of dichloromethane.
Following the above crystallization procedure, 0.72 g of the
product was obtained as a second crop. The combined yield
of the title product 7-TES-10-desacetylbaccatin III, as a

5   white solid (m.p. 238-240°C), was 6.10 g (93%).
Elemental Analysis (%)

$C_{35}H_{50}O_{10}Si$

	Calcd.	Found
C	63.80	63.76
H	7.65	7.66

10 mp: 239 - 242°C

$[\alpha]_D$: -53.7 (c 1.0, $CHCl_3$)

TLC: R_f = 0.53 (silica gel, 50% EtOAc in hexane); UV and PMA
visualization. HI = 98.9%

15

(ii)   [2aR-(2aα,4β,4aβ,6β,9α,11β,12α,12aα,12bα)]-
6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,-
4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-
9,11-dihydroxy-4a,8,13,13-tetramethyl-
20   4-[(triethylsilyl)oxy]-7,11-methano-1H-
cyclodeca[3,4]benz[1,2-b]oxet-5-one
(7-O-TES-baccatin III)

25
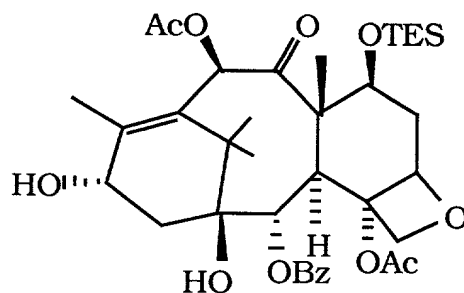
7-O-TES-10-desacetylbaccatin III prepared in step (i)
above (21.4 g, 32.4 mmol) was added to a flame-dried, argon
purged 1L 3-necked flask (equipped with a mechanical stirrer

and a digital thermometer) and dissolved in THF (350 ml, freshly distilled from sodium/benzophenone). The resulting solution was cooled to -70°C. A solution of n-butyllithium (n-BuLi, 14.6 ml of a 2.56 M solution in hexanes, 37.3 mmol,

5   titrated in triplicate with diphenylacetic acid in THF at 0°C) was added dropwise over a period of 23 minutes. The temperature of the reaction did not rise above -68°C during the addition. Solids were formed upon the addition of n-BuLi and did not appear to dissolve at

10   -70°C. The resulting mixture was stirred at -70°C for 20 minutes and was then warmed to -48°C. (A clear homogeneous solution was obtained upon warming to -48°C.) After stirring at -48°C for 1/2 hour, acetic anhydride (4.6 ml, 49 mmol, distilled (137 - 138°C, 1 atm) under an

15   atmosphere of argon before use) was added dropwise over 7 minutes. The temperature of the reaction did not rise above -45°C during the addition. The resulting solution was stirred at -48°C for 20 minutes and then at 0°C for 1 hour. The solution was diluted with ethyl acetate (350 ml), washed

20   with saturated aqueous NH_4Cl (250 ml), and the layers were separated. The aqueous layer was extracted with ethyl acetate (200 ml). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated on a rotovap. (All concentrations on the

25   rotovap were conducted with a water bath temperature of 35°C.) Exposure of the semi-solid to high vacuum (~1.5 mm Hg for 1/2 hour) gave 24.7 g of a white solid. The crude product was dissolved in CH_2Cl_2 (300 ml) and the volume of the resulting solution was reduced to ~70 ml on a rotovap.

30   Crystallization began within one minute. The mixture was allowed to stand at room temperature for 45 minutes, and then in a 4°C cold room for 18 hours. The crystals were filtered, washed with 1:9 CH_2Cl_2/hexanes (3 x 100 ml) on a suction filter, and dried under high vacuum (~0.2 mm Hg for

50

19 hours) to give 20.9 g (92.0%) of the title product as
fine white needles. The mother liquor was concentrated on a
rotovap and the residue was crystallized from CH_2Cl_2/hexanes
to give 0.82 g (3.6%) of the title product as small white

5   crystals. Crystallization was conducted as follows: The
residue was dissolved in CH_2Cl_2 (10 ml) and the volume of
the resulting solution was reduced to ~5 ml on the rotovap.
After standing at room temperature for 1/2 hour, no crystals
had formed. Hexanes (5 ml) were added in 1 ml portions and

10   the solution was swirled. A few crystals were present by
this time. The mixture was allowed to stand at room
temperature for 1/2 hour (more crystals formed) and then in
a 4°C cold room for 18 hours. The crystals were filtered,
washed with 1:9 CH_2Cl_2/hexanes on a suction filter, and

15   dried under high vacuum (~0.15 mm Hg for 21 hours).

The combined yield for the two crops was 95.6%.

mp: 218 - 219°C (decomp.)

$[\alpha]^{22}_D$: -78.4° (c 1.0, CHCl$_3$)

5 TLC: R$_f$ = 0.37 (silica gel, 1:9 acetone/CH$_2$Cl$_2$); visualized
by phosphomolybdic acid/ethanol.

The following Examples 9 to 11 demonstrate the
coupling of a preferred oxazolidine carboxylic acid of the
10 formula III or VII with a C-13 hydroxyl-bearing taxane of
the formula IV.

<u>EXAMPLE 9</u>

<u>Preparation of [2aR-</u>
15 <u>(2aα,4β,4aβ,6β,9α(4S*,5R*),11α,12α,12aα,12bα]]-3-Benzoyl-</u>
<u>2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid 6,12b-</u>
<u>bis(acetyloxy)-12-(benzoyloxy)-</u>
<u>2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-</u>
<u>4a,8,13,13-tetramethyl-5-oxo-4-[(triethylsilyl)oxy]-7,11-</u>
20 <u>methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester</u>
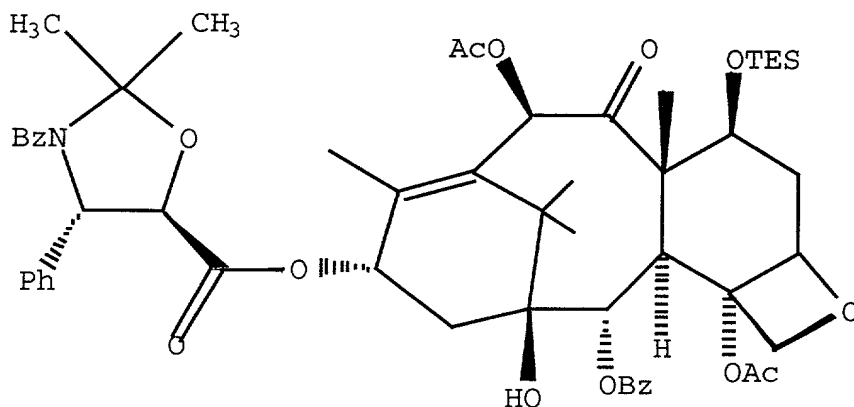
7-Triethylsilylbaccatin III (156 mg), the title
25 product of Example 6 (94 mg), toluene (0.6 ml), DCC (69 mg)
and DMAP (27 mg) were mixed together and the resulting

52

mixture was heated at 80°C for 3 hours. TLC at that time
showed complete consumption of the 7-triethylsilylbaccatin
III starting material and the appearance of a new spot. The
reaction mixture was diluted with CH_2Cl_2 (20 ml), saturated

5 aqueous $NaHCO_3$ (10 ml) was added, the H_2O layer was
extracted with CH_2Cl_2 (2 x 10 ml) and the combined organic
layers were dried over anhydrous $MgSO_4$. Upon concentration
in vacuo some precipitate was formed which was removed by
filtration. The compound was purified by preparative HPLC

10 (hexane:ethyl acetate, 2:1) to give 214 mg (96%) of the
title product.

Mass spec.: $M+H^+ = 1,008$

TLC (hexanes/ethyl acetate = 1:1) Rf = 0.56

m.p. = 164-165°C

15 ^1H NMR in accordance with the above structure.

The above procedure was repeated on a larger scale
employing 7-triethylsilylbaccatin III (475 mg), the title
product of Example 6 (287 mg), toluene (1.8 ml), DCC (210
mg) and DMAP (50 mg). HPLC chromatography yielded 666 mg

20 (98%) of the title product.

EXAMPLE 10

Alternative Preparation of [2aR-

(2aα,4β,4aβ,6β,9α(4S*,5R*),11α,12α,12aα,12bα]-3-Benzoyl-

25 2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid 6,12b-

bis(acetyloxy)-12-(benzoyloxy)-

2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-

4a,8,13,13-tetramethyl-5-oxo-4-[(triethylsilyl)oxy]-7,11-

methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester

30

A suspension of the title product of Example 6 (103
mg), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (65 mg)
having the structure:

53
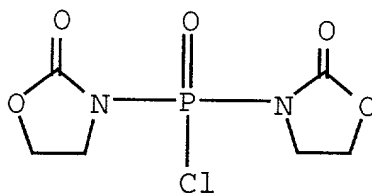
and 7-triethylsilylbaccatin III (170 mg) in CH_2Cl_2 (0.5 ml)
and TEA (0.068 ml) was stirred at room temperature for 3
hours. After 1/2 hour the suspension became a somewhat
cloudy solution. No reaction was observed by TLC. The
mixture was then heated under reflux for 1 hour (no
reaction). At that time, DMAP was added and heating
continued for 1 hour resulting in product formation. The
mixture was diluted with ethyl acetate, washed with
saturated aqueous $NaHCO_3$, pH 3 phosphate buffer, saturated
aqueous NaCl, dried and evaporated to give 232 mg (95%) of
the crude product. ^{1}H NMR showed the desired title product
and about 2 to 5% starting material. (Product
characteristics consistent with structure of Example 9.)

EXAMPLE 11
Preparation of [2aR-
(2aα,4β,4aβ,6β,9α(4S*,5R*),11α,12α,12aα,12bα]]-3-Benzoyl-2-
methoxy-4-phenyl-5-oxazolidinecarboxylic acid 6,12b-
bis(acetyloxy)-12-(benzoyloxy)-
2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-
4a,8,13,13-tetramethyl-5-oxo-4-[(triethylsilyl)oxy]-7,11-
methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester

54
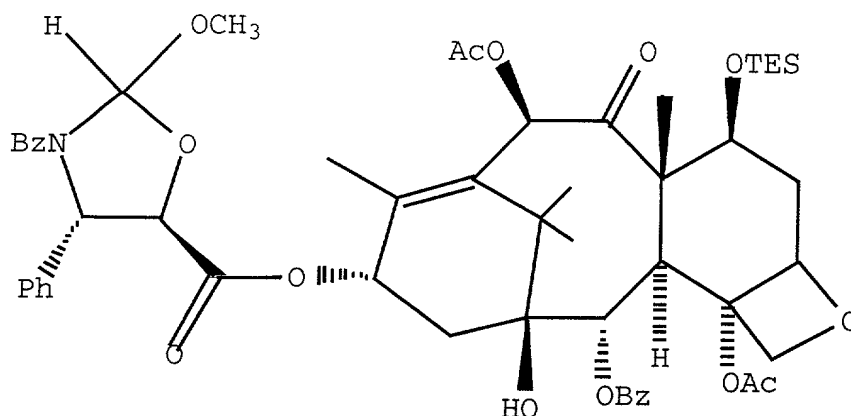
7-Triethylsilylbaccatin III (255 mg), the title
product of Example 7 (155 mg), toluene (1.0 ml), DCC (113
mg) and DMAP (27 mg) were mixed together and the resulting
mixture was heated to reflux (about 80°C) for 1 hour. At
that time, the reaction was not complete and a second charge
of DCC (56.5 mg) and DMAP (13.5 mg) were added and the
mixture was refluxed for another 2 hours. Small amounts of
starting material still remained. After work-up (dilution
with EtOAc, washing with saturated aqueous $NaHCO_3$, and
drying with anhydrous $MgSO_4$), the product was purified on
preparative HPLC. The main fractions gave 300 mg (82%) of
the title product (and a small amount of impurity).

On a larger scale, 7-triethylsilylbaccatin III (1.022
g), the title product of Example 7 (620 mg), DCC (451 mg)
and DMAP (107 mg) were mixed together in a dry flask and
suspended in toluene (3.5 ml). The mixture was heated at
80°C for 1 hour, then another 0.5 eq. of the title product
of Example 7 was added, followed by a second charge of DMAP
(107 mg) and DCC (451 mg). Starting material still remained
after heating for 1 hour. The reaction mixture was heated
overnight and worked-up as described above. Purification on
HPLC (hexane:ethyl acetate, 9:1 → 1:1) gave as the first
fraction 75 mg of an impurity, then the title product (928

mg, 65%). 213 mg of starting material (21%) remained. The product was a mixture of diastereomers (not separated). TLC (hexanes/ethyl acetate = 1:1) Rf = 0.51
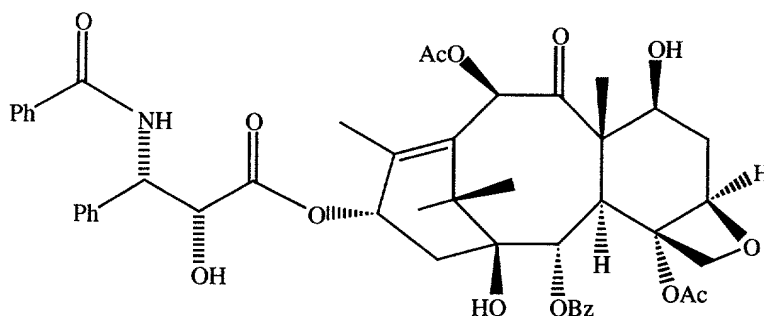
m.p. (mixture) = 152-155°C

5   ^{1}H NMR in accordance with the above structure.

The following Examples 12 to 13 demonstrate ring opening of preferred coupled products of the formula V or VIII to yield a C-13 acyloxy sidechain-bearing taxane of the

10   formula VI.

<u>EXAMPLE 12</u>
<u>Preparation of Paclitaxel</u>

15

The title product of Example 11 (106 mg) was dissolved in THF (1.5 ml) and cooled to 0°C. 10% aqueous HCl (0.5 ml) and acetic acid (0.5 ml) were added. The

20   reaction mixture was stirred at 0°C for 5 hours. It was then stirred for 2 hours at room temperature, followed by storage overnight at 4°C. As the reaction was still not complete, the mixture was then stirred at room temperature for 5 hours after which time no starting material was

25   detectable by TLC. After work-up (dilution with EtOAc, washing with saturated $NaHCO_3$ and brine, and drying with $MgSO_4$), it was purified by preparative HPLC (hexane:ethyl

56

actetate, 5:1 → 1:2) to give 70 mg (78%) of the title
product. (Product characteristics consistent with those of
an authentic sample of the natural product.)

5   EXAMPLE 13

                        Preparation of Paclitaxel

      The title product of Example 9 (0.084 mmol) was
dissolved in acetone (1.0 ml), Pd(CH3CN)$_2$Cl$_2$ (0.5 mg) was
10   added (from tip of spatula), and the mixture was stirred at
room temperature. After 2 hours, deprotection of the 7-
triethylsilyl group was observed to a small extent
(additional polar spots on TLC were observed). Further
stirring gave additional deprotection of the 7-triethylsilyl
15   group, although some starting material still remained.
Another portion of Pd(CH3CN)$_2$Cl$_2$ (0.5 mg) was added and
stirring was continued overnight. At this time, paclitaxel,
the starting acetonide taxane and an analog of the starting
acetonide taxane in which the 7-position triethylsilyl group
20   had been deprotected to form a hydroxyl group were observed
by TLC. A third portion of Pd(CH3CN)$_2$Cl$_2$ (0.5 mg) was added
and stirring was continued for 8 hours (deprotecting the 7-
position triethylsilyl group; at this time, a small amount
of starting material remained with amounts of impurities
25   more polar than paclitaxel). The reaction mixture was
quenched with saturated NaHCO$_3$, worked up by diluting with
ethyl acetate, washing with H$_2$O followed by saturated
aqueous NaCl, and drying with anhydrous MgSO$_4$. The solvents
were removed *in vacuo* and the residue was purified by HPLC
30   (hexane:ethyl acetate, 2:1 → 1:2) to yield 30 mg (42%) of
the title product (paclitaxel). (Product characteristics
consistent with those of an authentic sample of the natural
product.)